The Menopausal Hot Flush – Anything New?

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Abstract:

Although the hot flush is generally recognised by women and the medical profession as the most characteristic and often a very distressing symptom of the climacteric, it remains an enigma. The physiological changes associated with the hot flush are different from any other flushing condition, with an increased peripheral blood flow, increased heart rate and in particular a decrease in galvanic skin resistance, which is unique to the flush. Flushing occurs as a result of disturbance of the temperature regulating mechanism situated in the hypothalamus, and probably a reduction in the thermoneutral zone, within which fluctuations of basal body temperature do not provoke compensatory vascular responses. Many factors have been implicated, including hormone releasing factors, gonadotrophins and neuro-humorals. However, the role of oestrogen is critical and the clinical value of oestrogen therapy is well established and has been confirmed by a Cochrane review. Nevertheless, the precise mechanism by which reduced circulating levels of oestrogen are involved in causing the flush has not yet been established.

Priming with oestrogen seems to be an essential pre-requisite for flushing, as young women with ovarian dysgenesis and very low circulating levels of oestrogen never have hot flushes unless they are given oestrogen replacement therapy, which is later discontinued. Oestrogen antagonist activity by selective oestrogen receptor modulators such as tamoxifen and raloxifene can also cause flushing. A link with gonadotrophins is demonstrated by a temporal association of flushes with the pulsatile release of luteinising hormone (LH). However, if LH pulses are eliminated by GnRH analogue, the frequency of flushing is not altered, which confirms that LH is merely associated with the flush rather than being causative.

It is probable that the flush is initiated by a supra-pituitary mechanism which is influenced by the hypothalamic factors responsible for pulsatile LH release. A variety of chemical pathways have been proposed involving serotonin, noradrenalin and dopamine. Trials of drugs that selectively inhibit the re-uptake of serotonin and noradrenalin have shown some beneficial effects, as also has gabapentin, but often the results have been disappointing, and certainly less than the response seen with oestrogen or tibolone.

The prevalence of hot flushes varies considerably around the world and is less in the Far East than in the west. Differences in diet and in particular the intake of phytoestrogens has been implicated and many studies have tried to establish whether dietary supplementation with phytoestrogens might be a suitable alternative to conventional hormone replacement therapy(HRT). So far, the results are disappointing. Other lifestyle measures such as avoiding alcohol, caffeine and spicy foods, keeping the core body temperature cool, paced respiration, taking exercise and even acupuncture may help.

Hot flushes remain a major cause of reduced quality of life in a large proportion of menopausal women, but perhaps because they are not fatal and are usually self-limiting, there has been rather limited research or clinical interest. However, for the increasing number of women being treated with tamoxifen for breast cancer, and for whom oestrogen will usually be contra-indicated or unsuitable, there is an urgent need to identify the underlying mechanism so that appropriate, specific and safe non-oestrogen therapy can be offered to improve their quality of life.

Introduction

The hot flush associated with the menopause is a unique symptom and causes considerable distress and impairment of quality of life. Although flushing occurs in some other conditions such as carcinoid syndrome, phaeochromocytoma, thyroid disease and the dumping syndrome, the associated physiological changes are not the same.

Around the world there is a considerable variation in prevalence ranging from 80% in Dutch women [1] to 0% among rural Mayan Indians in Mexico [2,3]. While differences in study design may account for some of this disparity in reported prevalence rates, there are also cultural and ethnic differences to consider. Rumours that Japanese women rarely experienced flushes due to their life-long high intake of soy products in their diet have not been supported by recent evidence [3-5]. In North America, African American women experience more troublesome vasomotor symptoms than white women [6]. Race-ethnicity-specific associations between vasomotor symptom reporting and specific polymorphisms for sex steroid metabolising enzymes and sex steroid receptors have also been reported [7]. It has been considered that women who are overweight are less likely to experience hot flushes due to peripheral conversion of androgens in the adipose tissue to oestrone. However, recent analysis from the Study of Women's Health Across the Nation (SWAN) has shown that a higher percentage of body fat is associated with an increased likelihood of reporting vasomotor symptoms [8], possibly due to more body insulation thereby maintaining a higher core body temperature.
Climate may be an important factor affecting the frequency of flushing. A meta-analysis of 54 studies demonstrated that, although climate plays a role in the variation of the prevalence of hot flushes, the incidence was not associated with mean temperature of the warmest month. The frequency appears to increase as the difference in temperatures between the hottest and coldest months increase. So women living in seasonal climates may have greater sensitivity to temperature changes [9].

Subjective Features

Hot flushes may occur at any time of the day or night and be triggered by a variety of common situations but in particular embarrassment, stress, sudden temperature change, alcohol, caffeine or any warm drink. These subjective features are variable but usually start with a sudden sensation of heat or warmth, often accompanied by sweating and reddening of the skin and sometimes palpitations. Most often this will start in the upper body or back and spread upwards or downwards, and sometimes all over the body. The perceived duration of a flush ranges from 30 seconds to 60 minutes with a mean between 3-4 minutes [10,11]. Prodromal symptoms are common and for many include a feeling of "increasing pressure in the head", though most women have difficulty in describing this sensation [12]. During the night a decrease of rapid eye movement (REM) sleep and waking often precedes a hot flush [13,14]. The frequency of flushes varies between individuals ranging from a few per month to several per hour. For clinical studies of the effect of treatments for hot flushes, regulatory authorities require the patients to have at least 50 hot flushes a week. For

most women the hot flushes will continue for more than one year, and for about 25% for more than 5 years. Occasionally women will still be experiencing flushes for up to 40 years [15].

The impact of hot flushes on the quality of life may be considerable and is probably often underestimated. Flushing interferes with work and daily activities as well as with sleep causing subsequent fatigue, loss of concentration, depression and all of this can interfere with family life as well as sexual function and partner relationships.

Physiological Changes

The subjective sensation of heat is the predominant feature of the flush. Temperature changes occur over a large portion of the body [16] and can be demonstrated by thermography [17] with temperature increases in the fingers and toes from about 20 to 33ºC [16,18,19]. As a result of the rise in peripheral body temperature there is a concomitant decrease in core temperature as recorded in the rectum and tympanic membrane [16]. Although the greatest temperature changes have been found in the fingers and toes, the symptom of flushing is usually experienced mainly in the face, neck and upper trunk, and it seems that the subjective sensation of heat is out of proportion to the actual temperature increase, which in these areas may be only about 1ºC [17]. Furthermore, the temperature increase often persists for several minutes after the sensation of warmth has passed, indicating that the flush is only experienced while the skin temperature is increasing. The severity of the sensation is therefore probably related more to the rate of temperature change than to actual temperature increase.

The increase in skin temperature results from a sudden peripheral vasodilatation, which has been demonstrated by plethysmography in the fingers, hands or arms [19,20]. See Fig. 1. This increased blood flow precedes the subjective sensation of the flush by at least one minute and persists for many minutes afterwards declining gradually along with the temperature. A rise in the heart rate, however, coincides with the sensation of flushing and usually returns to normal almost as quickly. Some women complain of palpitations before or during a flush, but no changes in cardiac rhythm have been found in flushing women who have had continuous 24 hour electrocardiograph (ECG) recordings [11]. However, fluctuation of the ECG baseline as shown in Fig. 1 has been a consistent finding at the onset of peripheral vasodilatation, and is probably due to a change in galvanic skin resistance as well as some sweating under the electrodes. A rapid and prolonged fall in skin resistance is also a characteristic feature and may be the first objective sign of an impending flush. Measurement of the skin resistance is probably the most reliable way of distinguishing a hot flush from other causes of peripheral vasodilatation [21], and for this purpose instruments are being designed to aid in the study of this condition [22].

Mechanism of Hot Flush

The hot flush is not easy to study. The human female is almost unique in experiencing this symptom, but animal models using monkeys and rats in which a surgical menopause has been induced, have provided some information [23], although how much this can be extrapolated to the human female is uncertain. The flush occurs as a result of a disturbance of the temperature regulating mechanism, which is situated in the hypothalamus. Many possible factors have been implicated including pituitary hormones, hormone releasing factors, gonadotrophins and neurohumoral pathways. A hormonal aetiology seems likely in view of the association of flushing with the climacteric, and the well-proven clinical value of oestrogen therapy in eliminating hot flushes [24], but the precise role that oestrogens play has yet to be established. A most attractive explanation of the mechanism at present is that from Robert Freedman [25], who has been one of very few recent investigators of the flush. See Fig.2. In the normal and asymptomatic woman there is a thermoneutral zone (about 0.4ºC), within which fluctuations of the core body temperature do not trigger compensatory mechanisms such as flushing or sweating. In the symptomatic woman the thermoneutral zone is considerably reduced, so that even minor fluctuations in core body temperature will reach the limits of the zone, and initiate a thermoregulatory response. The narrowing of the zone may be due to elevated central noradrenergic activation and probably precipitated by changes in oestrogen.

The association of flushing with the decline in oestrogen around the menopause is not clearly understood and indeed there are many situations that seem inconsistent with an oestrogen deficiency aetiology. Pre-pubertal girls have low circulating oestrogen levels but do not experience hot flushes, whereas they may occur in pregnancy when there is a high level of oestrogen production. Many women will pass through the climacteric without experiencing any hot flushes and there is no apparent difference in the oestrogen levels of these women compared with those who do flush [26,27]. Flushes are more prevalent in women who experience acute oestrogen withdrawal, such as following bilateral oophorectomy, than in those experiencing the gradual ovarian failure of a physiological climacteric. In addition, hot flushes are often the first symptom of the climacteric and do not usually persist in to the later postmenopause years when circulating oestrogen levels are very low.

Priming with oestrogen may be an essential pre-requisite for flushing, as young women with ovarian dysgenesis do not have hot flushes unless they are given oestrogen replacement therapy, which is later discontinued. Furthermore, infertile women taking clomiphene therapy may also complain of flushes, perhaps due to the anti-estrogenic action of the drug at the hypothalamus.

Gonadotrophins

Both primary and secondary ovarian failure are associated with elevated secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH), but only women with secondary amenorrhoea experience flushing. Gonadotrophin therapy given to infertile women does not provoke hot flushes and conversely flushes have been reported in women with pituitary insufficiency [28]. Although there is no difference in overall levels of FSH and LH between postmenopausal women who flush and those

who do not, a temporal association of flushes with the pulsatile pituitary release of LH has been demonstrated [29]. However, further studies in which the LH pulses were eliminated by an LHRH analogue without affecting the frequency of flushing episodes, confirm that LH is merely associated with the flush rather than being causative [30]. It is possible that neuroendocrine events in the hypothalamus which govern the pulsatile release of LHRH may be linked functionally with thermoregulation, as some of the hypothalamic neurones that contain LHRH are closely related, anatomically at least, to the pre-optic anterior nuclei that regulate body temperature [31].

Serotonin

In recent years there has been increasing interest in the potential role of serotonin or 5-hydroxytriptomine (5-HT) in the mechanism of flushing. Serotonin is involved in many functions including mood, anxiety, memory, sleep, sexual and eating behaviour, and after the menopause the blood levels decrease by about 50% and oestrogen therapy restores these levels. There are multiple serotonin binding sites and at least three different types. Activation of 5-HT 1α causes hypothermia and activation of 5-HT 2α causes hyperthermia [32]. The interaction of oestrogen 5-HT and other neurotransmitters may be explained by the following sequence of events:

- Oestrogen enhances the synthesis of 5-HT and endorphins.
- Endorphins and 5-HT inhibit the production of noradrenalin.
- The withdrawal of oestrogen in the climacteric is associated with decreasing levels of endorphin and 5-HT and an increase in 5-HT receptors.
- This results in a loss of the feedback mechanism of noradrenalin production causing an increase in noradrenalin, which may reduce the thermoneutral zone and thereby increase the likelihood of flushing.
- Therefore any substance that increases 5-HT, oestrogen, endorphins or decreases noradrenalin may widen the thermoneutral zone and therefore be expected to reduce hot flushes.

The effectiveness of several selective serotonin re-uptake inhibitors (SSRI) agents in the treatment of hot flushes has been studied with paroxetine and venlafaxine showing the most promise. However, they do not suppress flushes as well as oestrogen and the side effects may limit their acceptability [33]. Most studies were in women treated for breast cancer and more long-term data are required from healthy women.

The anticonvulsant gabapentin has been studied in randomised placebo controlled trials and has even been shown to have a similar effect to conjugated equine oestrogens in one small study [34]. However, the mechanism of action is unknown and side effects are quite common [33,35].

Alternative therapies

With the widespread alarm about the supposed risks of hormone replacement therapy (HRT) induced by the media in particular, the atmosphere has been ripe for promotion of alternative therapies and complimentary medicines, which claim that because they are not HRT they must be safer. Phyto-oestrogens are substances produced from

plants with weak estrogenic and anti-estrogenic activity. Red clover isoflavones have been the subject of several trials of which five out of six randomised controlled trials showed no improvement in hot flushes [33]. Soy Isoflavones have also shown mixed results with most trials showing no improvement in hot flushes and gastrointestinal side effects are common. However, they may induce endometrial hyperplasia [36], which does indicate some estrogenic activity. Black cohosh does not seem to demonstrate any significant benefit over placebo, and in one study the patients preferred placebo to Black cohosh [37]. Furthermore, the possible mechanism of action of Black cohosh is largely unknown although there may be some binding to oestrogen receptors, there is a wide variation between and within products and there have now been several reports of liver failure requiring transplantation and other disturbance of liver function [38,39]. Many of these preparations are promoted as being "natural" with the evidently false assumption that this implies absence of risk [40].

Women treated with acupuncture have reported a reduction of more than 50% in their hot flushes, but most studies are of poor quality with an inadequate control method. There is certainly a need for a large double-blind, randomized, controlled trial comparing acupuncture with HRT and a credible placebo acupuncture in order to provide reliable evidence [41].

An alternative licensed medication, which has been available for many years is Clonidine. This is an alpha-adrenergic agonist that may reduce peripheral vascular reactivity. Around half of the several randomised controlled trials have shown a reduction in the frequency and severity of hot flushes by between 1 and 2 hot flushes per day [33,40], but side effects such as dry mouth, visual disturbance, drowsiness and insomnia are quite common.

In all studies of the treatment of hot flushes, the placebo response is powerful and significant and in a Cochrane analysis of HRT trials it ranged from 31-59%, one of the highest for any medication [24,42]. Thus any alternative therapy must be properly measured against a placebo in an appropriately designed randomized trial [43].

None of the alternatives are as effective as oestrogen or tibolone, and few have been studied beyond a few weeks, so that whatever efficacy they may have, is unknown in the long term as well as their safety [40,44].

Lower dose HRT and progestogens

Regulatory authorities are recommending the use of the lowest effective dose of hormone therapy regimens and for the shortest duration. Recent studies have demonstrated that doses as low as conjugated equine oestrogens 0.3mg daily [44], oral oestradiol 0.5mg [45] and transdermal oestradiol 14μg daily [46] can be significantly more effective than a placebo, and when combined with a progestogen the effects seem to be even greater.

Progestogens alone, such as norethisterone [48], megestrol [49] and medroxyprogesterone acetate [50] have also been shown to reduce flushes, though their potential for causing adverse events has to be considered [44].

Life-style measures

For women with mild hot flushes, simple life-style measures such as keeping the core body temperature cool, avoiding alcohol, caffeine and spicy foods, taking regular exercise and using paced respiration [51] may be sufficient to reduce the severity and frequency of flushing satisfactorily. But, severe and frequent flushes that significantly

impair quality of life will need specific treatment for which conventional HRT is by far the most potent. Following the early reports from the Women's Health Initiative and the exaggerated scares about HRT in the media, women are being falsely informed that 'Bioidentical hormone therapy (BHT) has all of the good effects of HRT with none of the severe side-effects that have caused so many women to avoid traditionally administered HRT'. In addition it is suggested that the dose of these hormones can be tailored to the individual based on measurement of salivary hormone levels. None of these claims are supported by scientific evidence such that The Endocrine Society [52], the International Menopause Society [53] and the U.S. Food and Drug Administration (FDA) [54] have all condemned this false advertising and cautioned women and their physicians about using BHT.

Terminology

It is important to have uniformity of scientific terminology, and the use of the term *flash* instead of *flush* by North American colleagues is both regrettable and inappropriate. The *Concise Oxford Dictionary* states that flash implies a sudden transitory blaze, whereas a flush implies a prolonged suffusion with a warm colour rather than a transient event. It is unlikely that this habit will change but any woman experiencing flushes will confirm that it is rarely over in a flash.

Discussion

Although the hot flush is the most characteristic and recognised feature of the climacteric, it is still poorly understood and the causative mechanism not yet established. It is a major cause of reduced quality of life for most women passing through this phase of their life and it is most regrettable that with the inappropriate reporting of the results of the WHI studies in particular, that so many women around the world have been denied the opportunity of easy and safe relief from these symptoms. In addition, there are many women suffering from flushes resulting from their treatment for breast cancer, for whom HRT will usually be considered inappropriate. It is for these women and others who are unable to take oestrogen, that suitable non-hormonal alternative therapies are urgently needed. For this we need to identify the underlying mechanism of flushing and more research in this area is required.

So there is not much new on this subject. The flush was studied much more in the 1970-80's than in recent years and the pace of research seems to have slowed, perhaps because it is a benign and self limiting symptom, but it is unique and remains the enigma of the menopause.

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Figures

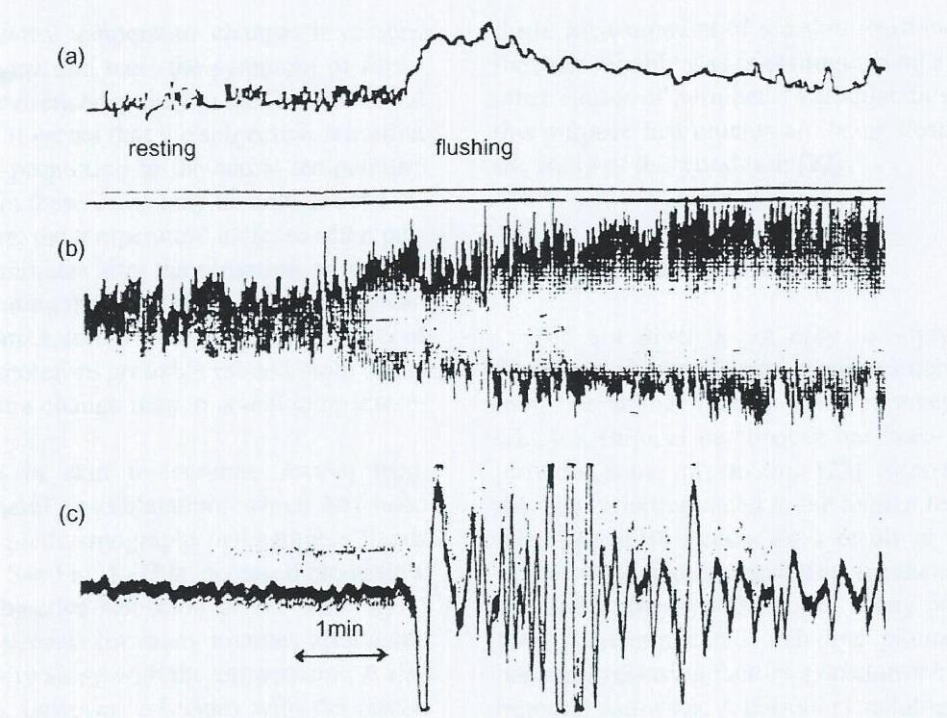

Figure 1: Physiological changes during a hot flush.

a) Heart rate.
b) Digital plethysmograph demonstrating the change in blood flow associated with a flush.
c) Single lead chest electrocardiograph record.

[From reference 20 with permission]

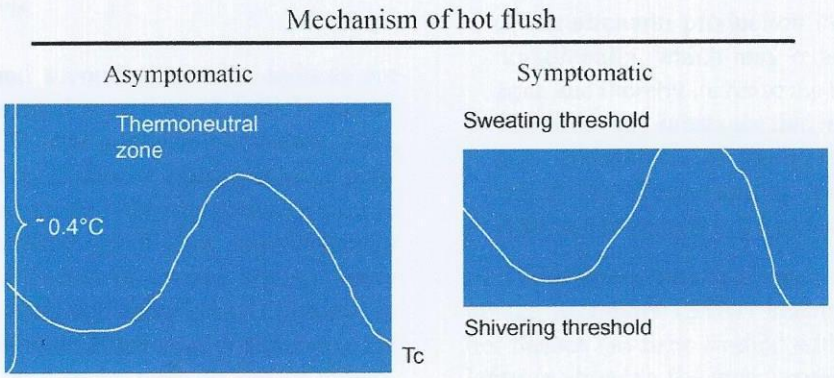

Fig. 2. Suggested mechanism for the hot flush; adapted from Ref. [25]. Central body temperature (T_c) fluctuates naturally. Decrease in thermoneutral zone or increase in T_c triggers temperature regulating mechanisms of peripheral vasodilatation, sweating or + shivering.